Commentary

The AVERT trial shows that a theoretically plausible intervention – intensive and very early mobilisation of stroke patients – begun as soon as possible after admission, is not better than existing protocols and may actually be harmful. This implies that the 22 existing guidelines worldwide on early stroke rehabilitation need to be rewritten. In fact, the AVERT trial suggests that very early mobilisation of stroke patients should be restricted to a few times in the first 24 hours and limited to small doses of 10 minutes at most. This restriction is particularly recommended for stroke patients with very severe neurological impairments (National Institutes of Health Stroke Scale > 16) and patients with haemorrhagic stroke.

The AVERT trial raises the question: why is applying a higher dose of out-of-bed therapy, slightly earlier, more harmful than a lower dose of shorter duration? Is the impaired regional cerebral blood flow in penumbral areas sensitive to orthostatic variation?[1,2] It may be assumed that, especially in severe and haemorrhagic strokes, the cerebrovascular autoregulation needed to sustain sufficient regional cerebral blood flow is impaired.[3,4] High doses of long-duration mobilisation very early after stroke, which often result in tired and drowsy patients slumping in their chairs, may further reduce the regional cerebral blood flow in critical penumbral and oligaemic brain areas, thus increasing neurological damage. Further research of patients with (hyper)acute stroke is now needed into the longitudinal association between dependence on body and head position and cardiac output on the one hand, and impaired cerebral haemodynamics and reduced cerebral perfusion on the other.

Although the AVERT trial suffers from some minor methodological problems such as contamination, as the usual care group started mobilisation earlier each year, the indirect message of this ground-breaking trial is that sufficiently powered Phase III trials are possible in complex interventions such as stroke rehabilitation.

Provenance: Invited. Not peer-reviewed.

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Commentary

After stroke, clinical practice guidelines recommend management in an acute stroke unit because there is strong evidence to indicate that this reduces death and disability.[1] Early mobilisation is proposed to be a contributing factor to these better outcomes;[2] however, this recommendation is not underpinned by evidence, and nor is early mobilisation clearly defined. This paper presents the primary results of the AVERT Trial, a large Phase III trial, which provides this evidence.

This study is a landmark clinical trial for physiotherapy for numerous reasons: it investigates physiotherapy intervention sequentially, with preliminary evidence gained across earlier Phase I and Phase II trials; it is a massive trial involving 56 hospitals across five countries, thus, findings are highly generalisable and provide a rich dataset for ongoing analysis; it shows that a complex, multidisciplinary intervention in stroke care can be undertaken in a trial considered high quality in terms of design, adherence, management and analysis; and it shows these trials can be performed and led by physiotherapists.

The results show that very early mobilisation reduces the odds of a favourable outcome at 3 months compared with usual care, which is contrary to our assumptions. The intervention arm received earlier mobilisation than the control (by 4.8 hours). Some may query the clinical impact of this difference, but there was a resultant difference in the primary outcome. To understand the importance of the timing, type and amount of early mobilisation, further analysis is required to investigate the change in usual care over the 8 years of the trial and the dose-response analysis. Investigation of these results will provide the evidence to inform optimal stroke unit care.

Some may be disappointed that the primary results are not in favour of very early mobilisation. They show that the phrase 'more is better' might not apply in this early timeframe. This is an important finding, despite being in a possibly surprising direction, and it challenges our assumptions, forces us to rethink and consider our practice more deeply.

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Author's response: where to next?

The AVERT trial was a labour of love for the hundreds of clinicians, researchers and patients involved. The collective vision of research excellence and discovery, of building the stroke rehabilitation and recovery evidence base was clear and ever present. So too was the shared value of collaboration, of participating in something that extended beyond our own national boundaries. It has been an exciting and demanding experience, and we have all learnt a lot.

These early, primary results from the trial have been surprising to many. Increasingly, over the last decade, early rehabilitation and mobilisation has been recommended, despite limited, albeit positive, evidence.[1] Over the long course of AVERT we witnessed (and more importantly, measured) a shift in practice to earlier intervention in usual care. It is unknown whether this reflects within-trial 'contamination' or the more global shift in practice. Large, pragmatic trials take time and AVERT took far longer than our collective wisdom suggested. We have indeed shown that global trials can be done, but it was tough. Our new insights into the major challenges of these trials cover planning for timely trial completion, which contains costs and maintains the trial's relevance in a shifting world, and the need for better funding mechanisms and broader collaboration to support global rehabilitation trials.

Despite, or perhaps because of, the shifting practice landscape, the results of AVERT are clear: doing too much too soon interferes with the recovery process. As further results emerge, clearer guidance for practice will be possible. The 'who', 'when' and 'how